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Short Communication

Non-Invasive Techniques for Liver Fibrosis Evaluation: The Role of Thrombomodulin and Elastography

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DESCRIPTION

Chronic Liver Disease (CLD) is a leading cause of morbidity and mortality worldwide, often progressing to liver cirrhosis, a condition characterized by extensive fibrosis and liver dysfunction [1]. One of the key challenges in managing CLD is accurately assessing the degree of liver fibrosis, which plays a critical role in determining disease prognosis and guiding therapeutic interventions. Traditionally, liver biopsy has been the gold standard for assessing liver fibrosis, but this invasive procedure is not without limitations, including risk of complications, sampling error and patient discomfort. Non-invasive techniques, such as elastography to measure liver stiffness, have gained significant attention as viable alternatives [2]. More recently, biomarkers that reflect both the degree of liver fibrosis and the underlying pathophysiological processes are being examined to complement these imaging techniques. Among these, thrombomodulin has recent as a potential alternative [3].

Thrombomodulin: A multifaceted biomarker

Thrombomodulin (TM) is a glycoprotein expressed primarily on the surface of endothelial cells, playing a pivotal role in the regulation of coagulation and inflammatory responses [4,5]. It serves as a cofactor for thrombin, converting it into an enzyme that activates protein C, which in turn inhibits clot formation and promotes fibrinolysis. Apart from its role in coagulation, TM has been implicated in modulating endothelial cell function, inflammation and fibrosis, processes that are critical in the progression of liver diseases.

In the context of liver disease, thrombomodulin levels can be influenced by endothelial damage, liver inflammation and fibrosis, all of which are central features of advanced chronic liver disease and cirrhosis. Elevated levels of thrombomodulin in the serum have been linked to the severity of liver damage and hepatic microvascular injury [6]. Furthermore, TM levels may correlate with liver fibrosis, reflecting not only the extent of liver injury but also the degree of vascular remodeling and endothelial dysfunction occurring in response to chronic liver inflammation and fibrosis.

Liver stiffness, typically measured by Transient Elastography (TE) or other non-invasive imaging modalities, is a well-established surrogate marker for liver fibrosis [7]. Increased liver stiffness is directly related to the accumulation of extracellular matrix components, including collagen, which is a characteristic of fibrosis. Since thrombomodulin is involved in endothelial function and the regulation of coagulation pathways, its association with liver stiffness represents a potentially valuable biomarker for assessing both liver fibrosis and the degree of microvascular damage in advanced CLD.

Several studies have demonstrated a significant correlation between elevated thrombomodulin levels and increased liver stiffness, suggesting that TM could be an adjunctive biomarker in the assessment of liver fibrosis [8-10]. For instance, in patients with cirrhosis, higher serum TM concentrations have been shown to correspond with higher liver stiffness values as determined by elastography. This relationship likely reflects the underlying pathophysiological mechanisms where endothelial dysfunction, microvascular injury and progressive fibrosis contribute to both the biochemical alterations (e.g., elevated TM) and the physical changes (e.g., increased stiffness) observed in the liver.

In addition to serving as a diagnostic tool, thrombomodulin levels may offer prognostic value. In liver cirrhosis, where the risk of portal hypertension, liver failure and Hepatocellular Carcinoma (HCC) increases, measuring TM could help identify patients at higher risk for complications [11]. The dynamic interplay between TM levels, liver stiffness and disease progression underscores the potential for thrombomodulin to be incorporated into routine clinical practice alongside elastography for more precise risk stratification.

Potential mechanisms behind the correlation

The correlation between thrombomodulin and liver stiffness in

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advanced CLD may be explained through several interrelated mechanisms. First, liver fibrosis is associated with microvascular damage and endothelial dysfunction, both of which can elevate thrombomodulin levels. Chronic liver injury leads to increased secretion of pro-inflammatory cytokines, activation of hepatic stellate cells and endothelial cell activation, all of which may upregulate the expression of thrombomodulin on endothelial cells. This upregulation is often a response to endothelial cell damage and the need to modulate coagulation and inflammatory pathways.

Additionally, the presence of portal hypertension, a common complication of advanced liver disease, can further exacerbate endothelial dysfunction, contributing to both elevated thrombomodulin levels and increased liver stiffness. This bidirectional relationship where inflammation and fibrosis promote endothelial injury and endothelial dysfunction exacerbates fibrosis creates a feedback loop that strengthens the association between thrombomodulin and liver stiffness.

The correlation between thrombomodulin and liver stiffness offers several clinical advantages. It provides a non-invasive, cost-effective means to assess both the structural and functional aspects of liver disease. While transient elastography remains a cornerstone for fibrosis assessment, the addition of biomarkers like thrombomodulin could enhance diagnostic accuracy, particularly in patients with non-cirrhotic liver diseases or those with overlapping conditions like Non-Alcoholic Fatty Liver Disease (NAFLD) or Alcoholic Liver Disease (ALD) [12].

Future studies should aim to further elucidate the role of thrombomodulin in liver disease progression and determine its potential utility in combination with other biomarkers. Longitudinal studies assessing the prognostic value of thrombomodulin, alongside liver stiffness measurements, could help establish its role in predicting clinical outcomes, including the risk of decompensation, liver-related complications and even HCC [13]. Additionally, investigating the therapeutic modulation of thrombomodulin expression or activity could open new avenues for treatment in advanced liver disease.

CONCLUSION

Thrombomodulin is recent as intriguing biomarker in the context of advanced chronic liver disease. Its correlation with liver stiffness suggests it could serve as both a diagnostic and prognostic tool, offering insight into liver fibrosis, endothelial dysfunction and the overall progression of liver disease. As non-invasive methods for liver assessment continue to evolve, incorporating thrombomodulin measurement alongside liver stiffness evaluations could significantly improve patient management, risk stratification and treatment outcomes in CLD.

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